Amendments to the Drawings

The attached sheets of drawings include changes to Figure 15C. In Figure 15C, a figure legend has been added.

Attachment: Replacement Sheet

Annotated Sheet Showing Changes

Remarks

Reconsideration of this Application is respectfully requested.

Claims 36-37 are pending in the application, with claim 36 being the sole independent claim. Claim 36 and Figure 15C are sought to be amended. Support for the amended claim can be found, *inter alia*, at page 11, line 16 to page 12, line 3; page 30, line 28 to page 31, line 12; and the claim as originally presented. Support for the amendment of Figure 15C can be found, *inter alia*, at page 14, lines 3-7 and the figure as originally presented. No new matter is added by way of these amendments. It is respectfully requested that the amendments be entered and considered.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Information Disclosure Statement

The Examiner has indicated that References AR52 and AR67 could not be located and has requested that Applicants submit copies of only these references in the response to the Office Action. *See* Paper No. 20060324 at page 2. As requested, Applicants have enclosed copies of References AR52 and AR67. It is respectfully requested that the Examiner initial and return a copy of the PTO-1449 submitted on June 10, 2004, and indicate in the official file wrapper of this patent application that these documents have been considered.

II. Specification

The Examiner has objected to the title of the invention as not descriptive. Applicants have amended the title as the Examiner suggested.

The Examiner has also objected to Figures 2C, 10 and 15C under 37 C.F.R. § 1.83. *See* Paper No. 20060324 at page 3. In regard to Figure 2C, the Examiner alleges that "...[t]he drawing depicts turbidometric analysis of pH effect on high concentrations of metal ion induced $A\beta_{1-40}$ (amyloid beta) aggregation," but that the specification at page 12, line 16 "...describes the proportion of soluble $A\beta_{1-42}$ remaining in the supernatant after incubation with high metal ion concentrations." Paper 20060324 at page 3. Applicants respectfully disagree with the Examiner, because page 12, line 16 of the specification reads that the "...proportion of soluble $A\beta_{1-40}$ remaining in the supernatant after incubation with various metal ions, where high metal ion concentrations were used."

In regard to Figure 10, the Examiner alleges that the "...[f]igure legends describing bars are duplicated [for example, +Zn(II)]..." Paper 20060324 at page 3. Applicants submit that the bars in the figure legend are not duplicated. The two bars labeled "+Zn(II)" in the figure legend correspond to data collected at two different pH values, and are listed in the figure legend below their corresponding pH values. For example, the striped bar symbol labeled "+Zn(II)" listed below the open square symbol labeled "pH 7.4", indicates that the addition of +Zn(II) occurred at pH 7.4. Likewise, the horizontally striped bar symbol labeled "+Zn(II)" corresponds to pH 6.5.

In regard to Figure 15C, Applicants submit herewith a Replacement Drawing to add a legend to Figure 15C.

In view of the information provided above, Applicants respectfully request that the Examiner reconsider and withdraw objections to the specification.

III. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 36 and 37 under 35 U.S.C. § 112, second paragraph as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *See* Paper No. 20060324 at page 4. Applicants have amended the preamble of claim 36 to recite a "candidate pharmacological agent." Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the indefiniteness rejection.

IV. Claim Rejections Under 35 U.S.C. § 102

The Examiner has rejected claim 36 under 35 U.S.C. § 102 as anticipated by Dyrks, T., *et al.*, "Amyloidogenicity of βA4 and βA4-bearing Amyloid Protein Precursor Fragments by Metal-catalyzed Oxidation," *Journal of Biological Chemistry*, 267(25): 18210-18217, 1992 ("Dyrks *et al.*"). *See* Paper No. 20060324 at page 4. Applicants respectfully disagree.

An anticipation rejection under 35 U.S.C. § 102 requires a showing that each limitation of a claim is found in a single reference, practice or device. *See In re Donohue*, 766 F.2d 531, (Fed. Cir. 1985). Claim 36 relates to a method for the identification of an

agent to be used in the treatment of Alzheimer's disease (AD), wherein the agent is capable of inhibiting redox-reactive metal-mediated crosslinking of amyloid beta (Aβ) comprising (a) adding a redox-reactive metal to a first Aβ sample; (b) allowing the first sample to incubate to allow Aβ crosslinking; (c) adding the redox-reactive metal to a second Aβ sample comprising a candidate pharmacological agent; (d) allowing the second sample to incubate for the same amount of time as the first sample; (e) removing an aliquot from each of the first and second samples; and (f) determining presence or absence of crosslinking in the first and second samples.

Dyrks *et al.* discusses the aggregation properties of A4CT, the C-terminal 100 residues of amyloid protein precursor (APP). Dyrks *et al.* indicates that incubation of A4CT with hemoglobin and H_2O_2 results in aggregation of A4CT. *See* Dyrks *et al.* at page 18212. Amino acids, vitamin C and trolox were found to inhibit hemoglobin/H_2O_2-induced aggregation of A4CT, suggesting that the aggregation of A4CT is catalyzed . *See* Dyrks *et al.* at page 18213. Dyrks *et al.* also discusses that hemoglobin and H_2O_2 cause aggregation of βA4. *See* Dyrks at page 18214. However, Dyrks *et al.* does not describe the addition of an agent to reduce or inhibit βA4 aggregation. Thus, Dyrks *et al.* does not teach the addition of an agent capable of inhibiting redox-reactive metal-mediated crosslinking of Aβ. Accordingly, Dyrks *et al.* does not teach every limitation of claim 36 and as a result does not anticipate claim 36.

Notwithstanding the forgoing discussion, Applicants submit herewith a Declaration Under 37 C.F.R. § 1.132 by Kevin J. Barnham, Ph.D. Dr. Barnham indicates that A4CT and Aβ have different chemical natures and likely give rise to differing arrays of oxidatively

modified products when subjected to metal catalyzed oxidation. (Barnham Declaration, ¶ 15 and 16.) Given the differing arrays of oxidatively modified products likely to be generated by metal catalyzed oxidation of A4CT and Aβ, Dr. Barnham indicates that different oxidation modifications are likely responsible for the observed hemoglobin- and H_2O_2-induced aggregation of A4CT and Aβ in Dyrks *et al.* (Barnham Declaration, ¶ 17.) Based on these differences, Dr. Barnham concludes that Dyrks *et al.* does not describe the method of the present claims which involves the addition of an agent capable of inhibiting redox-reactive metal-mediated crosslinking of Aβ, or create a reasonable expectation of success for the method of the present claims. (Barnham Declaration, ¶ 19.)

In view of the information provided above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 36.

V. Claim Rejections Under 35 U.S.C. § 103

The Examiner has rejected claim 37 under 35 U.S.C. § 103 as unpatentable over Dyrks *et al.* *See* Paper No. 20060324 at page 5. Applicants respectfully traverse this rejection.

A *prima facie* case of obviousness cannot be established unless all of the claim elements are taught or suggested by the cited references. *See In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974); *see also In re Glaug*, 283 F.3d 1335, 1341-42 (Fed. Cir. 2002); *In re Rijckaert*, 9 F.3d 1531, 1533 (Fed. Cir. 1993).

An element of the currently presented claims is a method comprising the addition of an agent capable of inhibiting redox-reactive metal-mediated crosslinking of Aβ. Applicants

maintain that Dyrks *et al.* does not teach or suggest such a method. *See* discussion set forth in Section IV, above.

Therefore, not all of the elements of the currently presented claims are taught or suggested by the cited references. Consequently, a *prima facie* case of obviousness has not been established. Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 37.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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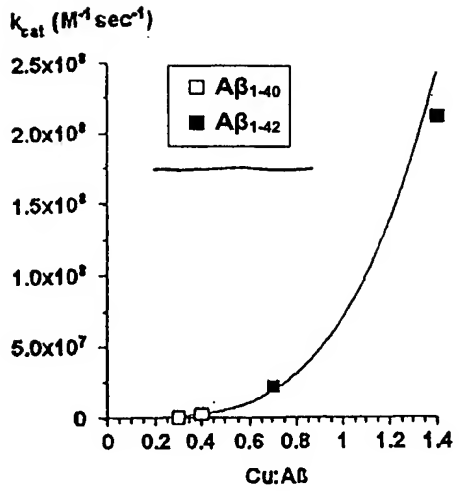
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$A\beta_{1-40}$
$A\beta_{1-42}$
0 0.2 0.4 0.6 0.8 1 1.2 1.4
Cu:Aß

Figure 1SC